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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BORGEEST, CHRISTINA M	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 09/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/796,486	MORSEY ET AL.	
	Examiner	Art Unit	
	Christina Borgeest	1649	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-25,34 and 37-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-25,34 and 37-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

Applicant's election of Group II, claims 17-25, 34 and 37-39 in the reply filed on July 28, 2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-16, 26-33, 35 and 36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on July 28, 2005.

Specification

The disclosure is objected to because of the following informalities: The first line of the specification should contain all the continuity data; the continuity data are missing from the specification. Appropriate correction is required.

The specification contains a typo on page 3, line 5: (□4-6kg/day). Appropriate correction is required.

Claim Objections

Claim 20 is objected to because of the following informalities: claim 20 contains a misspelling of the word "releasing". Appropriate correction is required.

Claim 25 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim can only depend upon on an independent claim or a singly dependent claim. See MPEP § 608.01(n).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17-25, 34 and 37-39 are indefinite because they are subject to more than one interpretation (see MPEP, 2143.03: "If a claim is subject to more than one interpretation, at least one of which would render the claim unpatentable over the prior art, the Examiner should reject the claim as indefinite under 35 U.S.C. 112, second paragraph"). Claims 17-21 (or in the case of claims 22-25, 34 and 37-39, depend upon claims that) recite "comprising the addition of...amino acids to the amino terminus of a 29 amino acid terminal fragment." The use of the word "comprising" leaves these claims open to interpretation because the addition of x number of amino acids to the N-terminus of a 29 amino acid terminal fragment reads on a peptide of any length, as long as the 29 amino acid fragment is present. In addition, claims 17-25, 34 and 37-39 are indefinite because there are no recited structural limitations, for instance, the GHRH variants could be cyclic or linear peptides. There is a precedent in the field for making

cyclic GHRH variants because they are more stable (for a review, see Campbell et al., 1995). Furthermore, claims 17-24 and 34 do not recite functional limitations of any kind, *i.e.*, the authors do not explicitly say how the claimed polypeptide functions compared to the native form. Rewriting the claims in precise terms would obviate this rejection.

Claims 17-20 and 25 are rejected under 35 U.S.C. 112, second paragraph, for being indefinite because they are subject to more than one interpretation. Applicant has used the term "amino terminus" in claims 17-20, rather than specifically name amino acid residue numbers in those claims to limit the interpretation of the phrase. Furthermore, claim 19 is indefinite because it is not clear whether applicant is referring to the *second amino acid in the polypeptide* or the *second amino acid addition* "is not Pro or Ala". Finally, in claim 25 Applicant recites, amino acids that are "naturally occurring", note however, the use of the phrase, "naturally occurring" could be interpreted to include D amino acids, for such amino acids are found in nature (See Fuji and Saito, Homochirality and Life; The Chemical Record. 2004;4:267-278). Rewriting the claims in precise terms would obviate this rejection.

Claims 21-24 are rejected under 35 U.S.C. 112, second paragraph because there is insufficient antecedent basis for limitation in the claims.

Claim 21 recites the limitation "comprising a substitution of Gly with Ala at residue 15". There is insufficient antecedent basis for this limitation in the claim, because there is no point of reference for the amino acid substitution. Although there is a high degree of homology among the GHRH amino acid sequences of various species, except for the case of human and swine, they are not identical (see Table I in Campbell

et al. Rational design, synthesis, and biological evaluation of novel growth hormone releasing factor analogues; Biopolymers. 1995;37(2):67-88). Changing the wording to indicate a reference point, for example, "[a] GHRH variant that differs from from SEQ. ID. NO: __ by substitution of a Gly with Ala at residue 15" would obviate this rejection.

Claim 22 recites the limitation "comprising a substitution of Leu with Ala at residue 22". There is insufficient antecedent basis for this limitation in the claim because there is no point of reference for the amino acid substitution. As previously stated, GHRH amino acid sequences are not identical in all species (Campbell et al.). Changing the wording to indicate a reference point, for example, "[a] GHRH variant that differs from from SEQ. ID. NO: __ by substitution of a Leu with Ala at residue 22" would obviate this rejection.

Claim 23 recites the limitation "comprising substitutions of Gly with Ala at residue 15 and Leu with Ala at residue 22". There is insufficient antecedent basis for this limitation in the claim, because there is no point of reference for the amino acid substitution. As previously stated, GHRH amino acid sequences are not identical in all species (Campbell et al.). Changing the wording to indicate a reference point, for example, "[a] GHRH variant that differs from from SEQ. ID. NO: __ by substitution of a Gly with Ala at residue 15 and Leu with Ala at residue 22" would obviate this rejection.

Claim 24 recites the limitation "comprising the addition of Gly and Arg at the carboxy-terminus". There is insufficient antecedent basis for this limitation in the claim, because there is no point of reference for the amino acid substitution. As previously stated, GHRH amino acid sequences are not identical in all species (Campbell et al.).

Changing the wording to indicate a reference point, for example, "[a] GHRH variant that differs from from SEQ. ID. NO: __ by addition of Gly and Arg at the carboxy-terminus" would obviate this rejection.

Claims 37-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 37-39 are drawn to a pharmaceutical composition, thus they are interpreted as product claims, however, all three claims contain the phrase " comprising administering to said animal...", which suggests a method claim. Deletion of the portion of the claims drawn to a method would obviate this rejection. Claims 37-39 are further rejected under 35 U.S.C. 112, second paragraph, because the claims contain claims contain the phrase, "administering to said animal an effective amount..." It is not clear in the claims whether the composition is effective to produce an immune response, nutritional response or some other physiological response. Although p. 22, lines 9-10 of the specification states, "[s]uch compositions will contain a therapeutically effective amount of the compound..." followed by dose ranges on page 22, line 36 and p. 23, line 1, applicant does not define what the in the claims what the *effect* of administration of the pharmaceutical compound would be.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 17-21, 25 and 37-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Campbell et al. (Rational design, synthesis, and biological evaluation of novel growth hormone releasing factor analogues Biopolymers. 1995;37(2):67-88). Campbell and colleagues teach several 29 amino acid GHRH variants with amino acid additions at the amino terminus (see p. 77, Table III). Claim 17 recites a GHRH variant comprising the addition of one amino acid to the amino terminus of a 29 amino acid amino terminal fragment. Claim 18 teaches the GHRH variant of claim 17, wherein the amino acid is a hydrophobic residue or a tyrosine. Valine is substituted at residue 2 in one of the variants listed in Table III, and valine is a hydrophobic amino acid. Claims 17 and 18, as written, are anticipated by Campbell et al. Claim 19 recites a GHRH variant comprising the addition of two or three amino acids to the amino terminus, wherein the second amino terminal fragment of GHRH is not Pro or Ala, and Campbell et al. teach several 29 amino acid GHRH variants with two or three amino acids to the amino terminus, wherein the second amino acid is neither Pro nor Ala. Claim 20 recites a GHRH variant of claim 19 comprising the addition of more than three amino acids to the amino terminus of a 29 amino acid terminal GHRH fragment wherein the addition does

not interfere with the functional activity of GHRH. Campbell et al. teach all the elements of claim 19, and on page 77, Table IV several GHRH variants with more than 3 additions in which the relative potency of the GHRH is increased. Note that the Examiner has interpreted the phrase, "does not interfere with the functional activity of GHRH" to mean "does not decrease" because there would be little value in inventing a GHRH variant that had less activity or the same activity as the native form. Thus, claim 20, as written, is anticipated by Campbell et al. Note that Applicant has used the term "amino terminus" in claims 17-20, rather than specifically name amino acid residue numbers in those claims to limit the interpretation of the phrases "amino terminus. By convention, short peptides are named from left (amino) to right (carboxyl), and the Examiner has given the claims their broadest reasonable interpretation to encompass all amino acid residues between the amino terminus and the midpoint of the peptide.

Claim 21 recites a GHRH variant further of claims 17, 19 or 20 further comprising a substitution of Gly with Ala at residue 15, and Campbell et al. teach all the elements of claims 17, 19 and 20 and several 29 amino acid GHRH variants with a substitution of Gly with Ala at residue 15. Thus, claim 21 is anticipated by Campbell et al. Claim 25 recites the GHRH variant of claim 18, 19 or 21 in which the amino acids are naturally occurring. Campbell et al. teach all the elements of claims 18, 19 or 21 and the naturally occurring amino acid variants (see Table III). Note however, the use of the phrase, "naturally occurring" could be interpreted to include D amino acids, for such amino acids are found in nature, thus claim 25, as written would also read on a 29 amino acid analog with a D-amino acid substitution.

Claims 37-39 are also anticipated by Campbell et al. Campbell and colleagues teach rational drug design of GHRH variants "with the goal of producing potent, long-acting bioactive peptides" (p. 68, column 1, 2nd paragraph) and all the elements of lciams 17, 19 and 20. Claims 37-39 recite a pharmaceutical composition comprising the GHRH variant of claim 17, 19 or 20. Claims 37-39, as written are anticipated by Campbell et al.

Claims 17 and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Martin et al. (Dipeptidyl peptidase IV (DPP-IV) from pig kidney cleaves analogs of bovine growth hormone releasing factor (bGRF) modified at position 2 with Ser, Thr or Val. Extended DPP-IV substrate specificity? 1993; Biochimica et Biophysica Acta. 1164:252-260). Claim 34 recites a purified polypeptide of GHRH variant of claim 17, 19 or 20. Martin et al. teach all the elements of claim 17, a GHRH variant with the addition of one amino acid to the amino terminus (see p. 502, Table 2) and the GHRH polypeptides taught by Martin et al. were purified see p. 500, Materials and Methods, column 2, 3rd paragraph). Thus, claim 34, as written, is anticipated by Martin et al. (1993).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell et al. (1995), in light of Zarandi et al. (Synthesis and *in vitro* and *in vivo* activity of analogs of growth hormone releasing hormone (GHRH) with C-terminal agmatine. Int. J. Peptide Protein Res 36, 1990, 499-505). Claim 22 recites a GHRH variant of claim 17, 19 or 20 further comprising a substitution of Leu with Ala at residue 22 and claim 23 recites a GHRH variant of claim 17, 19 or 20 comprising a substitution of Gly with Ala at residue 15 *and* Leu with Ala at residue 22. Campbell et al. describe GHRH variants of claims 17, 19 or 20 comprising a substitution of Gly with Ala at

residue 15, and containing only naturally occurring amino acids. Campbell et al. state that a "position 15 substitution with a helix-stabilizing, hydrophobic residue such as...Ala (for native Gly^{15}) GH-releasing potency is nearly equal to 4-fold in vitro," (see p. 72, column 1, 1st paragraph). Campbell et al. also state the advantages of making GHRH variants with L amino acid composition (see p. 76, column 1, 3rd paragraph): "[t]he advantage of this strategy was largely economical, since nonamidated, natural amino acid sequence analogues could be produced on a large scale using current DNA methods. The feasibility of recombinant [hGHRH] was rapidly demonstrated using both *E. coli* and *S. cerevisiae*." Campbell et al. do not describe a GHRH variant comprising a substitution of Leu with Ala at residue 22. Zarandi et al. (1990) describe the substitution of Leu with Ala at residue 22 (see p. 502, Table 2). Zarandi and colleagues stated that an Ala substitution at position 22 showed increases in vitro activities, for instance, analog MZ-2-165 has a relative potency of 4.7 times that of hGHRH(1-29)NH_2 (p. 502, Table 2). Analog MZ-2-165 also had in vivo GH releasing activities of 1.9 (after 5 minutes) and 2.05 (after 15 minutes) times that of hGHRH(1-29)NH_2 (p. 504, Table 4) in the rat. Although, Zarandi et al. used GHRH analogs with non-naturally occurring amino acid substitutions, their success in making a GHRH analog with a substitution of Leu with Ala at residue 22 with greater activity could be feasibly combined with the teachings of Campbell (GHRH variants with natural L-amino acid substitution of Gly with Ala at residue 15 leading to higher activity). Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the combination of Campbell and Zarandi's teachings resulting in the manufacture of a

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest whose telephone number is 571-272-4482. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

Christina Borgeest, Ph.D.
09/19/05

ELIZABETH KEMMERER
PRIMARY EXAMINER